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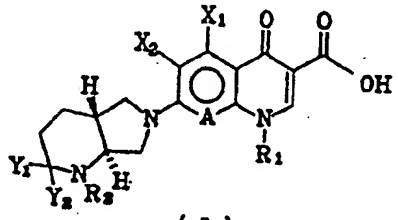
(54) Title: NOVEL QUINOLONE DERIVATIVES AND PROCESSES FOR PREPARING THE SAME



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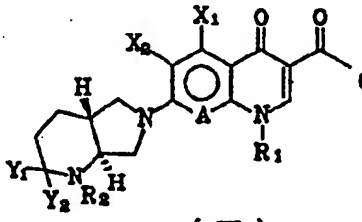

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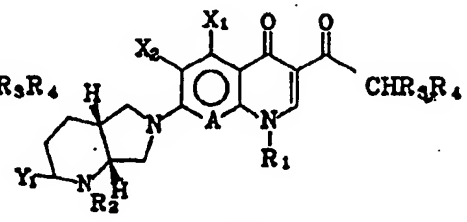

(IV)

(57) Abstract

The present invention relates to novel quinolone derivatives of formulae (I), (III) and (IV) having a broad antibacterial spectrum and to processes for preparing the same: wherein X_1 represents hydrogen, amino group, chloro, fluoro, or methyl; X_2 represents hydrogen or halogen; Y_1 and Y_2 each represent hydrogen, or lower alkyl (C_{1-3}) group; R_1 represents ethyl, cyclopropyl, halogen(F, Cl)-substituted cyclopropyl or halogen-substituted phenyl; R_2 represents hydrogen, methyl, ethyl or *t*-butoxycarbonyl; R_3 and R_4 each represent hydrogen, nitro group, methoxycarbonyl group, ethoxycarbonyl group or nitryl group; and A represents nitrogen atom, methyn group, fluoromethyn group, chloromethyn group, methoxymethyn group, or methylmethyn group.

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Novel Quinolone Derivatives and Processes for Preparing the Same

Technical Field

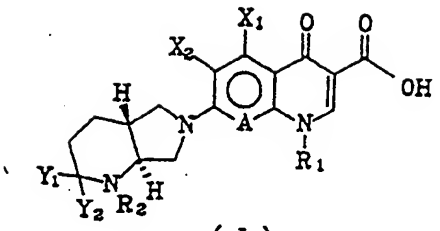
The present invention relates to novel quinolone derivatives which have a broad antibacterial spectrum, and processes for preparing the same.

Bacground Art

Nalidixic acid developed in 1963 is the first one of quinolonecarboxylic acid-type antibacterials. Quinolonecarboxylic acid-type antibacterials are known to exhibit strong antibacterial activity against aerobic *Gram-negative* bacteria and have been effectively used as a treatment for urethritis. Among these quinolone carboxylic acid-type antibacterials, especially norfloxacin, ciprofloxacin, ofloxacin, etc. are clinically used. However, these prior art compounds suffer from the disadvantage that they have drastically inferior antibacterial activity against *Gram-positive* bacteria, while they have superior antibacterial activity against *Gram-negative* bacteria. Especially, these quinolone-type antibacterials are known to have weak antibacterial activity against *Gram-positive* bacteria such as *Staphylococcus* or *Enterococcus* which show high resistance to sepem-type or ß-lactam-type antibacterial agents.

Disclosure of Invention

The present invention provides novel quinolone derivatives of formula (I), (III) and (IV) below and processes for preparing the same.



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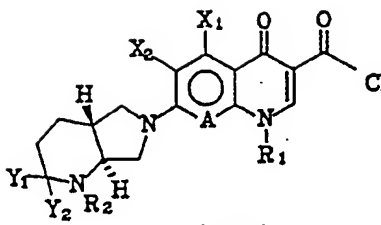

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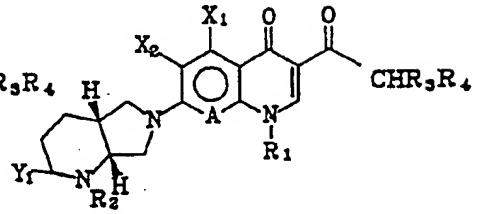


(IV)

wherein,

X_1 represents hydrogen, amino group, halogen such as chloro, fluoro, or lower alkyl such as methyl;

X_2 represents hydrogen or halogen;

Y_1 and Y_2 each represents hydrogen, or lower alkyl (C_{1-3}) group;

R_1 represents a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms or a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms which is substituted with a halogen atom, a phenyl group or a phenyl group substituted with one or two halogen atoms;

R_2 represents hydrogen, or lower alkyl such as methyl, ethyl;

R_3 and R_4 each represent hydrogen, nitro group, methoxycarbonyl group,

ethoxycarbonyl group or nitryl group; and

A represents nitrogen atom or -C=,

|

Y

in which Y represents hydrogen, halogen, lower alkyl or alkoxy or together with R_1 forms $-CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-OCH_2CH_2-$, $-OCH_2CH(CH_3)-$, $-SCH_2CH_2-$, or $-SCH_2CH(CH_3)-$.

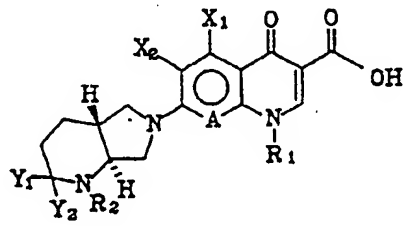
A is preferably nitrogen, methyn, fluoromethyn, chloromethyn, methoxymethyn, or methylmethyn.

Lower alkyl is preferably C_{1-6} alkyl, more preferably C_{1-4} alkyl, such as methyl or ethyl. X_2 halogen is preferably fluorine.

R_1 is preferably ethyl, cyclopropyl, halogen (F, Cl)-substituted cyclopropyl or halogen substituted phenyl.

The present invention is described in detail hereinbelow.

The present invention provides novel quinolone carboxylic acid derivatives of formula (I), and specifically, to novel quinolone carboxylic acid derivatives of formula (I) below which have trans-2,8-diazabicyclo[4.3.0]nonane derivatives represented by the formula (II) at 7-position of quinolone nucleus and possess a broad spectrum of potent antibacterial activities, and to processes for preparing the same.

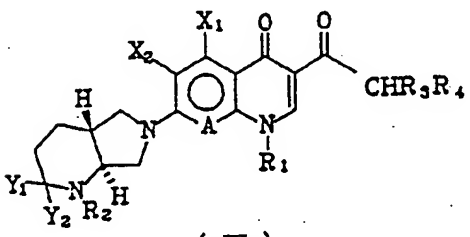


(I)

wherein,

X_1, X_2, Y_1, Y_2, R_1, R_2, and A are the same as defined above.

The present invention also provides novel quinolone carboxylic acid derivatives represented by the formula (III) and (IV) including mixtures thereof which show a broad spectrum of potent antibacterial activities, and to processes for preparing the same.



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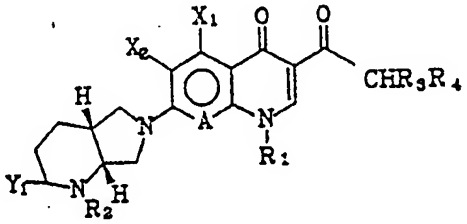
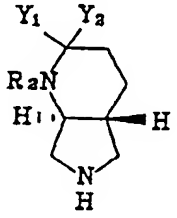


(IV)

wherein,

X_1, X_2, Y_1, Y_2, R_1, R_2, R_3, R_4, and A are the same as defined above.

The present invention provides trans-2,8-diazabicyclo[4.3.0]nonane derivatives represented by the formula (II) which are used as a side chain at 7-position of novel quinolone carboxylic acid derivatives (I) and processes for preparing the same.

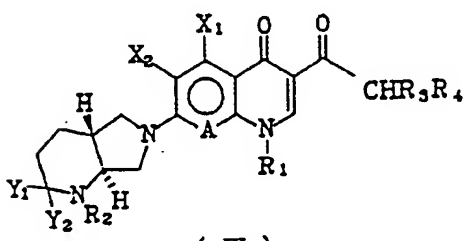


(II)

wherein,

Y_1, Y_2, and R_2 are the same as defined above.

The present invention also provides novel quinolone carboxylic acid derivatives represented by the formula (III) and (IV) including mixtures thereof which show a broad spectrum of potent antibacterial activities, and to processes for preparing the same.



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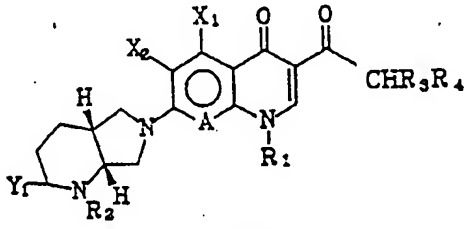
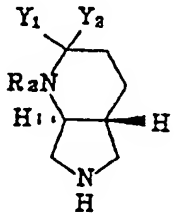


(IV)

wherein,

X_1, X_2, Y_1, Y_2, R_1, R_2, R_3, R_4, and A are the same as defined above.

The present invention provides trans-2,8-diazabicyclo[4.3.0]nonane derivatives represented by the formula (II) which are used as a side chain at 7-position of novel quinolone carboxylic acid derivatives (I) and processes for preparing the same.

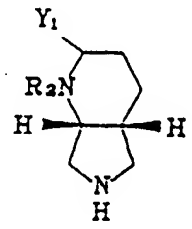


(II)

wherein,

Y_1, Y_2, and R_2 are the same as defined above.

The present invention also provides novel processes for preparing *cis*-2,8-diazabicyclo[4.3.0]nonane derivatives represented by the following formula (V) which are used as a side chain at 7-position of formula (IV) above.



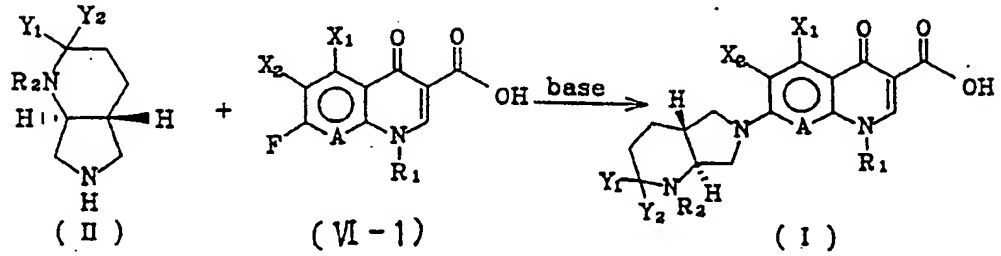
(V)

wherein,

Y_1 and R_2 are the same as defined above.

Quinolone derivatives of formula (I) according to the present invention may be prepared by condensing optionally protected *trans*-2,8-diazabicyclo [4.3.0]nonane derivatives of formula (II) above with the known compound of formula (VI-1) (P.D.Fernandes, "International Telesymposium on Quinolone", J.R.Prous Science, Barcelona, Spain, 1989. 1-143) in a solvent, in the presence of an inorganic or organic base, as described in the process (A). Inorganic bases used in this process include potassium carbonate and the like. Organic base used herein include diazabicyclo[5.4.0]undecene (DBU), pyridine, triethylamine and the like. The above reaction may be carried out at a temperature between room temperature and 150°C. The reaction time is about 1 to 10 hours.

Process (A)



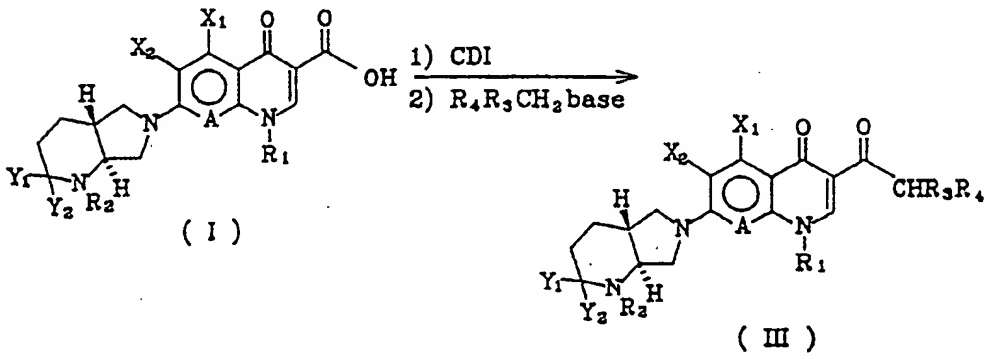
(II) (VI - 1) (I)

wherein,

X_1, X_2, Y_1, Y_2, R_1, R_2, and A are the same as defined above or R_2 is a protecting group such as *t*-butoxy carbonyl which is removed subsequently.

Also, quinolone derivatives represented by formula (III) of the present invention may be prepared by the following process (B). That is, the compound of formula (III) can be prepared by stirring compound of formula (I) and an activating agent such as carbodiimidazole (CDI) under reflux in the presence of a solvent such as chloroform, tetrahydrofuran (THF) and the like and then stirring nitromethane, diethylmalonate, dimethylmalonate, ethylnitrylacetate under reflux together with solution treated with a base such as sodium hydride, calcium carbonate, sodium carbonate in the presence of a solvent such as THF, and the like.

Process (B)



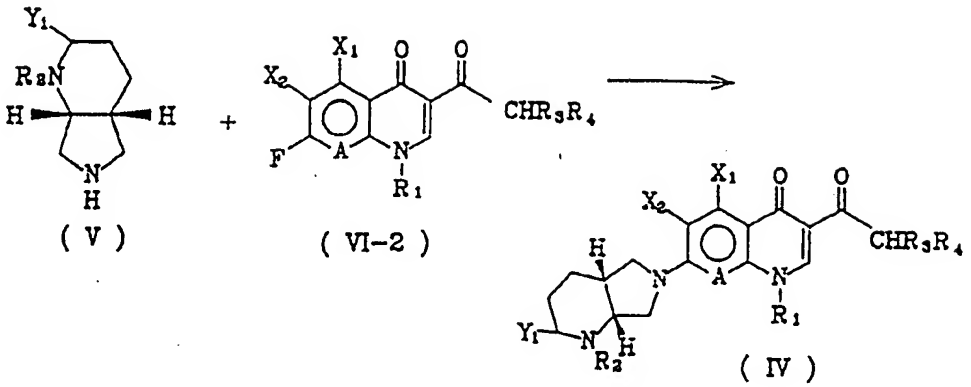
(I) (III)

wherein,

X_1, X_2, Y_1, Y_2, R_1, R_2, R_3, and R_4 are the same as defined above; and represent nitro group, nitryl group, diethoxycarbonyl group, or dimethoxycarbonyl group, and thereafter optionally interconverting R_3 and R_4.

Quinolone derivatives represented by formula (IV) of the present invention may be prepared by the following process (C). That is, the compound of formula (IV) can be prepared by reacting optionally protected *cis*-2,8-diazabicyclo[4.3.0]nonane derivatives of formula (V) with the compound of formula (IV-2) under reflux stirring in a solvent of acetonitrile or dimethylformamide (DMF) in the presence of basic, neutral, or acidic alumina.

Process (C)



(V) (VI-2) (IV)

wherein,

X_1, X_2, Y_1, R_1, R_2, R_3, and A are the same as defined above or R_2 is a protecting group such as *t*-butoxy carbonyl which is removed subsequently.

Novel quinolone derivatives of formula (IV) above can be also prepared by stirring the condensed compound with the solution under reflux. The condensed compound may be prepared by reacting *cis*-2,8-diazabicyclo[4.3.0]nonane derivatives of formula (V) with the known compound of formula (VI-2) in a solvent in the presence of an organic or inorganic base. Organic base used herein include diazabicyclo[5.4.0]undecene(DBU), pyridine, triethylamine and the like. Inorganic bases used in this process include potassium carbonate and the like. The above reaction may be carried out at a temperature between room temperature and 150°C. The reaction time is about 1 to 10 hours. The above solution is prepared by stirring carbodiimidazole under reflux in a solvent such as chloroform, tetrahydrofuran, and then stirring nitromethane, diethylmalonate, dimethylmalonate, ethylnitrylacetate under reflux with a base such as sodium hydride, calcium carbonate, sodium carbonate in a solvent such as tetrahydrofuran and the like.

The compounds of formula (I), (III) and (IV) above can be converted to the pharmaceutically acceptable salts thereof according to the conventional method. For example, these compounds can be converted to salts of inorganic acid such as hydrochloric acid, sulfuric acid, and phosphoric acid or salts of organic acid such as methansulfonic acid, lactic acid, oxalic acid, and acetic acid.

Trans-2,8-diazabicyclo[4.3.0]nonane derivatives of the following formula (II) according to the present invention can be prepared by the following Process (D). The Process(D) comprises the following four steps:

Step (1):

The compound of formula (VIII) can be prepared by reacting the known compound of formula (VII) (J.Org.Chem. 48, 1129 (1983)) with ß-alanine derivatives in the presence of ethanol under reflux;

Step (2):

The compound of formula (IX) can be prepared by cyclizating the compound of formula (VIII) with alkoxide such as sodium ethoxide or potassium *t*-butoxide at room temperature in the aromatic solvent such as benzene, toluene;

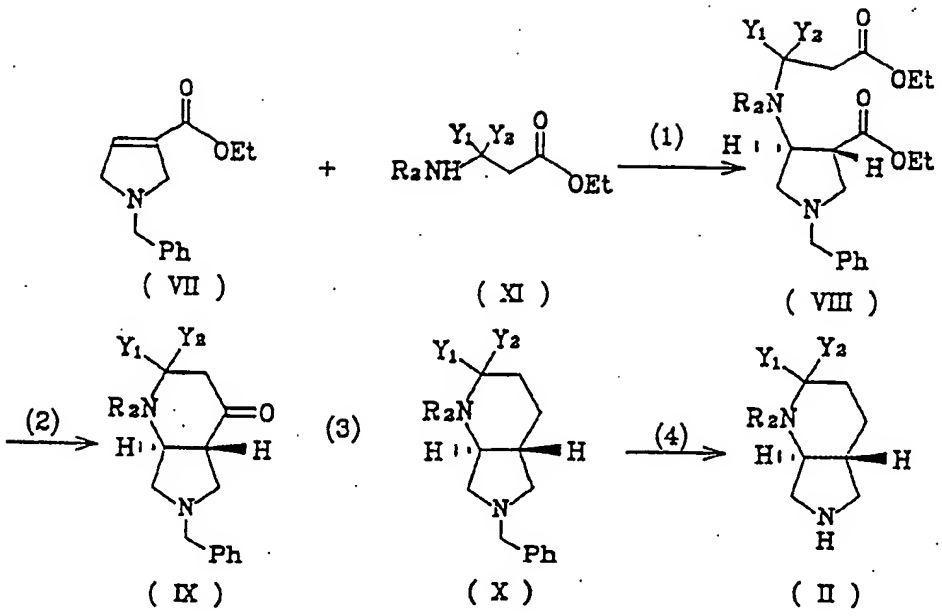
Step (3):

The compound of formula (X) can be prepared by reacting the carbonyl compound of formula (IX) with tosylhydrazine in a solvent of ethanol or methanol to obtain tosylhydrazone and then, by reducing the resulting compound with sodium shanobrohydride; and

Step (4):

The compound of formula (II) can be prepared by debenzylating the compound of formula (X) in methanol solvent in the presence of a catalyst of palladium or platinum.

Process (D)



wherein,

Y_1, Y_2, and R_2 are the same as defined above.

Trans-2,8-diazabicyclo[4.3.0]nonane derivatives of the following formula (II) according to the present invention can also be prepared by the following Process (E). The Process(E) comprises the following seven steps:

Step (5):

Trans isomer of formula (XIII) can be prepared by reacting the known compound of formula (XII) (UK Patent No. 1,086,637, or Chemical Abstract, 68, 96695W) with ß-alanine derivatives in the presence of ethanol under reflux;

Step (6):

Cis isomer of formula (XIV) can be prepared by reacting *trans* isomer of formula (XIII) with methansulfonyl chloride or lithium chloride, in methylene chloride or chloroform, in the presence of an organic base such as triethylamine or diisopropylethylamine, at the temperature between 0°C and 60°C;

Step (7):

Trans isomer of formula (XV) can be prepared by reacting *cis* isomer of formula (XIV) with potassium cyanate or sodium cyanate in DMF solvent;

Steps (8) and (9):

The compound of formula (IX) can be prepared from the compound of formula (XV) by the same method as Step (2) of Process (D) above;

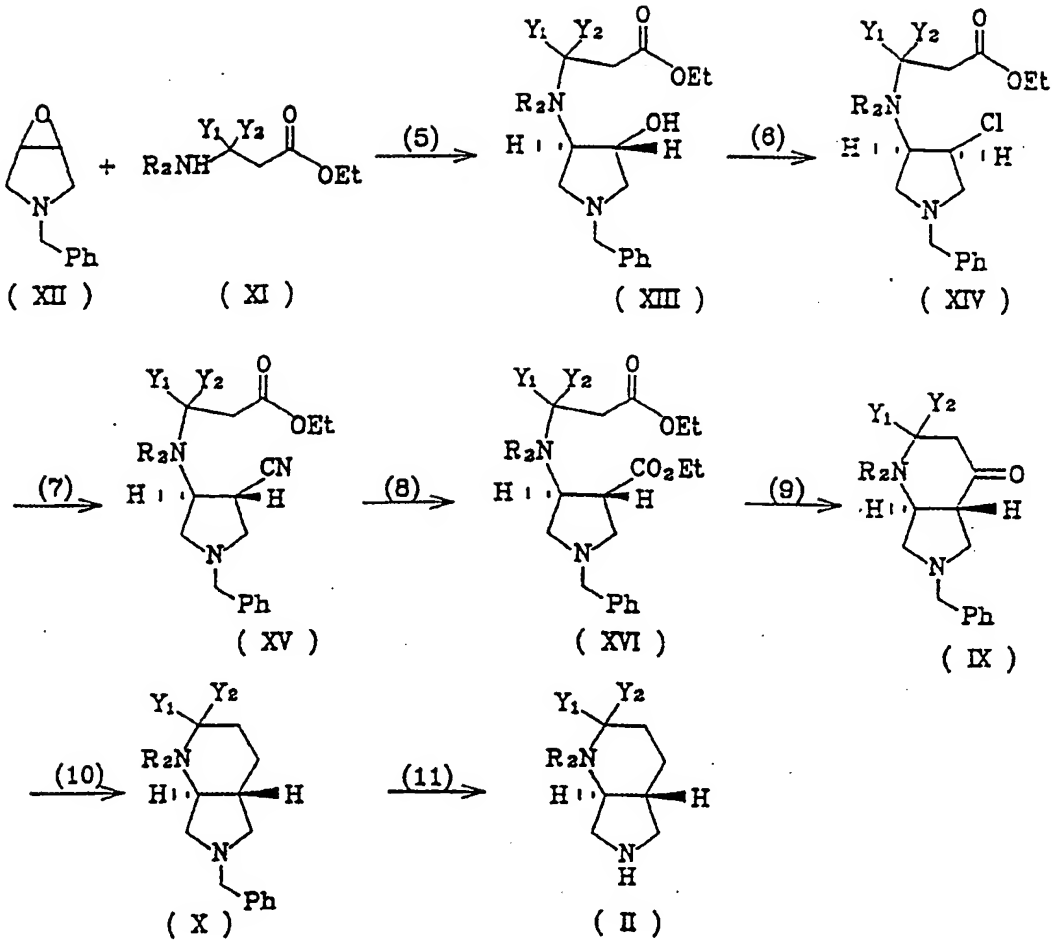
Step (10):

The compound of formula (X) can be prepared by reducing the compound of formula (IX) with zinc amalgam in the presence of hydrochloric acid; and

Step (11):

The compound of formula (II) can be prepared from the compound of formula (X) by the same method as Step (4) of Process (D) above.

Process (E)



wherein,

Y_1, Y_2 and R_2 are the same as defined above.

Cis-2,8-diazabicyclo[4.3.0]nonane derivatives of the formula (V) according to the present invention can be prepared by the following Process (F). The Process(D) comprises the following seven steps:

Step (12):

The ester compound of formula (XVIII) can be prepared by suspending

conventional pyridine derivatives of formula (XVII) in methanol and adding thionylchloride thereto and then stirring the resulting compound under reflux;

Step (13):

Alcohols of formula (XIX) can be prepared by reducing the compound of formula (XVIII) with lithium aluminum hydride in ethylether or THF;

Step (14):

The compound of formula (XX) can be prepared by chlorinating, brominating, or methane sulfonylating alcohols of formula (XIX);

Step (15):

The cyclized compound of formula (XXI) can be prepared by reacting the compound of formula (XX) with tocylimide and sodiumhydride in DMF;

Step (16):

Amines of formula (XXII) can be prepared by hydrolyzing the compound of formula (XXI) with 48% of hydrobromic acid;

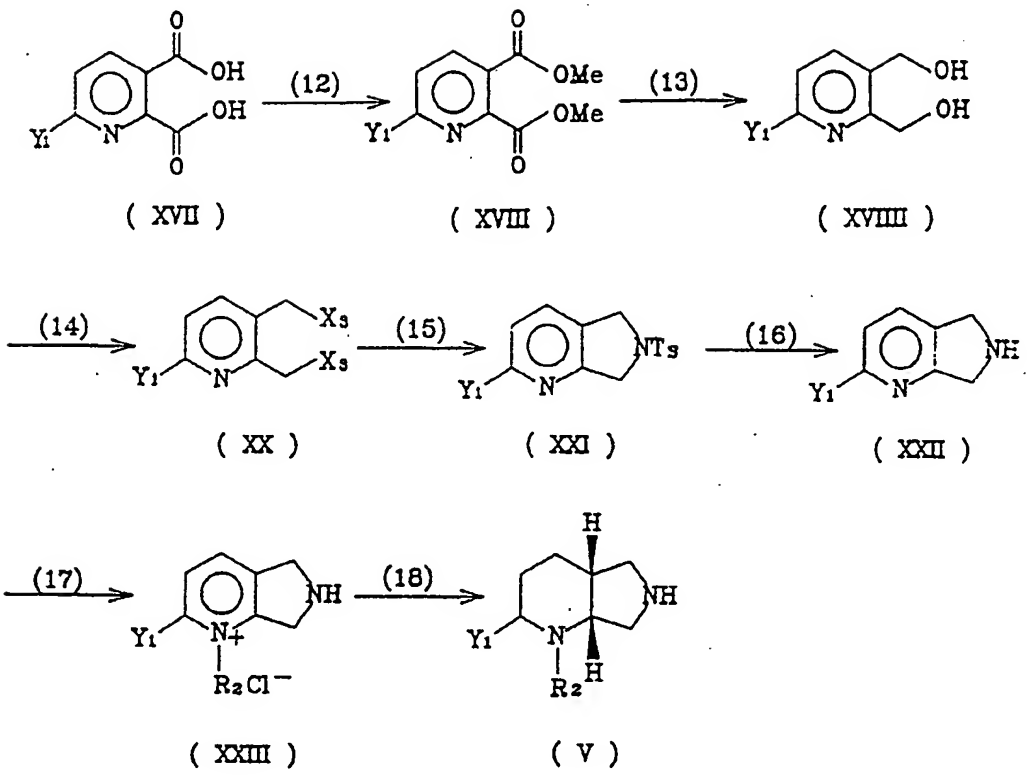
Step (17):

Salts of pyridine of formula (XXIII) can be prepared by reacting amine compounds of formula (XXII) with methaneiodide and acid anhydrous in a solvent of methylene chloride or ethyl alcohol; and

Step (18):

Cis-2,8-diazabicyclo[4.3.0]nonane derivatives of formula (V) can be prepared by hydrogenating the compound of formula (XXIII) in a solvent of methanol or ethanol in the presence of a catalyst of palladium or platinum.

Process (F)



(XVII) (XVIII) (XVIIII)

(XX) (XXI) (XXII)

(XXIII) (V)

wherein,

X_3 represents chloro, bromo, or methanesulfonyloxy group; and

Y_1 and R_2 are the same as defined above.

The following examples are intended to further illustrate the present invention, without limiting the scope of the invention.

Example 1: Preparation of *trans*-piperidinopyrrolidine

1) Preparation according to Process (D)

i) Preparation of *trans*-1-benzyl-3-carboethoxy-4-[N-benzyl-N-(2-carboethoxy)ethyl]aminopyrrolidine

A mixture of 23.9g of 1-benzyl-3-ethoxycarbonyl-3-pyrroline and 19.2g of ß-N-benzylalanine ethylester were added to 100*ml* of ethanol and stirred under reflux for 3 days. The solvent was evaporated under reduced pressure and then the residual product was purified by a silica gel column chromatography (nucleic acid-ethylacetate (3:1)) to give 26.9g of the above title compound (yield: 65%).

^{1}H-NMR($CDCl_3$, δ): 2.21(2H, m), 2.51(2H, m), 3.10-4.01(6H, m), 3.71(6H, s), 7.25(10H, m)

ii) Preparation of *trans*-N,N′-dibenzyl-2,8-diazabicyclo[4.3.0]-5-oxononane

20.5g of *trans*-1-benzyl-3-carboethoxy-4-[N-benzyl-N(2carboethoxy) ethyl]aminopyrrolidine was dissolved in 200ml of toluene and the reaction mixture was cooled in ice bath and then 6.1g of potassium *t*-buthoxide was added dropwise thereto. After adding dropwise, the reaction mixture was heated to 40°C and stirred for 4 hours. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in water. The resulting product was neutralized with aqueous solution of sodium bicarbonate, extracted with ethylacetate and then dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residual product was purified by a silica gel column chromatography to give 11.8g of the above title compound (yield: 71%).

^{1}H-NMR($CDCl_3$, δ): 2.30-3.0(9H, m), 3.20-3.70(2H, q), 3.50(6H, s), 3.4(1H, q), 7.15(10H, m)

iii) Preparation of *trans*-N,N′-dibenzylpiperidinopyrrolidine

15.9g of *trans*-N,N′-dibenzyl-2,8-diazabicyclo[4.3.0]-5-oxononane and 9.3g of tosyl hydrazine was added to 100ml of ethanol and then dehydrated with Dean-Stark distillation apparatus. 14g of sodium borohydride was added thereto and the mixture was stirred for 4 hours. The solvent was evaporated under reduced pressure and then the residue was extracted with ethylether. The mixture of ethylether was

evaporated under reduced pressure and then the residual product was purified by a silica gel column chromatography (nucleic acid-ethylacetate (3:1)) to give 13.2g of the above title compound (yield: 87%).

^{1}H-NMR($CDCl_3$, δ): 1.54-2.01(5H, m), 2.74-3.10(7H, m), 3.20-3.70(4H, m) 7.30(10H, m)

iv) Preparation of *trans*-piperidinopyrrolidine dihydrochloride

13.15g of *trans*-N,N′-dibenzylpiperidinopyrrolidine were dissolved in 50ml of methanol and then 1.0g of 10% Pd/C and 60ml of 30% methanol were added thereto. The resulting solution was hydrogenated by Parr hydrogenation reactor and debenzylated. The reaction mixture was filtered through celite and the filtrate was evaporated under reduced pressure. The residue was dissolved in 10ml of methanol and ethylether was added dropwise to the mixture. The resulting mixture was solidified and filtered to give 7.43g of the above title compound (yield: 93%).

^{1}H-NMR($CDCl_3$, δ): 1.50-1.90(5H, m), 2.74-3.01(7H, m)

2) Preparation according to Process (E)

i) Preparation of *trans*-1-benzyl-3-hydroxy-4-[N-benzyl-N-(2-carboethoxy) ethyl]aminopyrrolidine

87.25g (0.5 mol) of 3-benzyl-6-oxy-3-azabicyclo[3.1.0]nucleic acid and 113.8g (0.51 mol) of 3N-benzylaminopropanoate were put into 200*ml* of pyridine and stirred under reflux for 3 days. The reaction mixture was evaporated under reduced pressure to remove pyridine and then the residue was subjected to a silica gel column chromatography (nucleic acid-ethylacetate (1:1)) to give 166.2g of the above title compound (yield: 87%).

^{1}H-NMR($CDCl_3$, δ): 1.26(3H, t), 2.24(2H, m), 2.50(2H, m), 3.90(1H, m), 3.10-4.0(9H, m), 4.20(2H, q), 7.23(10H, m)

ii) Preparation of *cis*-1-benzyl-3-chloro-4-[N-benzyl-N-(2-carboethoxy)ethyl]

aminopyrrolidine

95.5g (0.25 mol) of *trans*-1-benzyl-3-hydroxy-4-[N-benzyl-N-(2-carboethoxy) ethyl]aminopyrrolidine and 70ml of triethylamine were dissolved in 1l of methylene chloride and 31.4g of methane sulfonyl chloride were added dropwise thereto at 0°C. 21.3g of anhydrous lithium chloride were added to the mixture and the reaction mixture was heated to 60°C and stirred for 20 hours. The reaction mixture was cooled, washed with water and dried over anhydrous magnesium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by a silica gel column chromatography (nucleic acid-ethylacetate (3:1)) to give 80.15g of the above title compound (yield: 82%).

^{1}H-NMR($CDCl_3$, δ): 1.26(3H, t), 2.24-2.52(4H, m), 3.10-4.0(9H, m), 4.14(1H, m), 4.20(2H, q), 7.30(10H, m)

iii) Preparation of *trans*-1-benzyl-3-cyano-4-[N-benzyl-N-(2-carboethoxy)ethyl] aminopyrrolidine

40.1g (0.1 mol) of *trans*-1-benzyl-3-chloro-4-[N-benzyl-N-(2-carboethoxy) ethyl]aminopyrrolidine and 7.8g of potassium cyanate were put into 100ml of DMF and the mixture was heated at 60°C for 14 hours while stirring. The reaction mixture was added to 400ml of ice water while stirring and the produced solid was filtered. The resulting solid was dissolved in ethylacetate and then the mixture was subjected to a silica gel column chromatography (nucleic acid-ethylacetate (3:1)) to give 30.5g of the desired compound (yield: 78%).

^{1}H-NMR($CDCl_3$, δ): 1.27(3H, t), 2.24(2H, m), 2.50(2H, m), 3.10-4.0(9H, m), 4.20(2H, q), 7.30(10H, m)

iv) Preparation of *trans*-1-benzyl-3-carboethoxy-4-[N-benzyl-N-(2-carboethoxy) ethyl]aminopyrrolidine

30.0g of *trans*-1-benzyl-3-cyano-4-[N-benzyl-N-(2-carboethoxy)ethyl] aminopyrrolidine were put into 300ml of 10% hydrochloric acid and the mixture was refluxed for 6 hours. After water was evaporated under reduced pressure, the residue

was heated and dried in vacuum drier for 10 hours. The residue was suspended in 200ml of methanol and 30ml of thionylchloride was added dropwise to the mixture while refluxing and further refluxed for 5 hours. The reaction mixture was evaporated under reduced pressure, the residue was put into methanol and 11g of sodium methoxide was added gradually thereto at 0°C. The resulting mixture was evaporated under reduced pressure again, dissolved in ethylacetate and washed with water. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure, and the residue was subjected to a silica gel column chromatography (nucleic acid-ethylacetate (3:1)) to give 30.5g of the title compound (yield: 61%).

^{1}H-NMR($CDCl_3$, δ): 2.21(2H, m), 2.51(2H, m), 3.10-4.01(6H, m), 3.71(6H, s), 7.25(10H, m)

v) Preparation of *trans*-N,N´-dibenzyl-2,8-diazabicyclo[4.3.0]-5-oxononane

20.5g of *trans*-1-benzyl-3-carboethoxy-4-[N-benzyl-N-(carboethoxy)ethyl] aminopyrrolidine was dissolved in 200ml of toluene and the reaction mixture was cooled in ice bath and then 6.1g of potassium *t*-buthoxide was added dropwise thereto. After adding dropwise, the reaction mixture was heated to 40°C and stirred for 4 hours. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in water. The resulting product was neutralized with aqueous solution of sodium bicarbonate, extracted with ethylacetate and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residual product was purified by a silica gel column chromatography to give 11.8g of the above title compound (yield: 74%).

^{1}H-NMR($CDCl_3$, δ): 2.30-3.0(9H, m), 3.20-3.70(2H, q), 3.50(6H, s), 3.4(1H, q), 7.15(10H, m)

vi) Preparation of *trans*-N,N´-dibenzyl-piperidinopyrrolidine

6.5g of zinc powder were put into 15ml of aqueous solution of 5% $HgCl_2$ and the mixture solution was shaken for 1 hour. The supernatant was removed and 9.6g

of N,N′-dibenzyl-2,8-diazabicyclo[4.3.0]-5-oxononane was added thereto. 10ml of 15% hydrochloric acid was added and the solution was heated while refluxing for 6 hours. While refluxing, 10ml of 5% hydrochloric acid was added several times. The mixture was cooled and 40ml of ethylacetate was added thereto and then supernatant of the mixture was removed. The suspension was filtered and the filtrate was neutralized with 5% KOH and extracted with ethylacetate. The extracted solution was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residual product was purified by a silica gel column chromatography (nucleic acid-ethylacetate (3:1)) to give 7.44g of the above title compound (yield: 81%).

^{1}H-NMR($CDCl_3$, δ): 1.54-2.01(5H, m), 2.74-3.10(7H, m), 3.2-3.70(4H, m), 7.30(10H, m)

vii) Preparation of *trans*-piperidinopyrrolidine dihydrochloride

6.12g (0.02 mol) of *trans*-N,N′-dibenzyl-piperidinopyrrolidine were dissolved in 30ml of methanol and then 0.5g of 10% Pd/C and 5ml of fumaric acid were added thereto. The resulting solution was hydrogenated by Parr hydrogenation reactor (initial hydrogen pressure: 60psi) to debenzylate. The reaction mixture was filtered through celite and the filtrate was evaporated under reduced pressure. The residue was dissolved in 10ml of 30% hydrochloride methanol and ethylether was added dropwise to the mixture. The resulting mixture was solidified and filtered to give 3.62g of the above title compound (yield: 92%).

^{1}H-NMR($CDCl_3$, δ): 1.50-1.90(5H, m), 2.74-3.01(7H, m)

Example 2: Preparation of *trans*-3-methyl-piperidinopyrrolidine dihydrochloride

According to the same method as i), ii), iii), iv), v), vi) and vii) of Process (E) in Example 1, 121g of methyl-3-(N-benzyl)aminobutanoate as a starting material was used to give 22.9g of the above title compound (total yield: 10.1%).

^{1}H-NMR($CDCl_3$, δ): 1.42-1.90(7H, m), 2.74-3.01(7H, m)

Example 3: Preparation of *cis*-piperidinopyrrolidine dihydrobromide

1) Preparation of 2,3-dimethoxycarboylpyridine

26.7g of 2,3-pyridinedicarboxylic acid were put into 500ml of methanol saturated with hydrogen chloride and the mixture was refluxed for 10 hours. Methanol was evaporated under reduced pressure and then the residual product was purified by a silica gel column chromatography (nucleic acid-ethylacetate (1:1)) to give 25.1g of the above pure title compound (yield: 85%).

^{1}H-NMR($CDCl_3$, δ): 3.95(6H, s), 7.34(1H, m), 7.51(1H, d), 8.84(1H, d)

2) Preparation of 2,3-dihydroxymethylpyridine

A solution prepared by dissolving 29.5g of 2,3-dimethoxycarbonylpyridine in 200ml of ethylether was added dropwise to a solution prepared by suspending 10g of lithium aluminum hydride in 300ml of dried ethylether at 0°C. This mixed solution was stirred at 20°C for 3 hours and 30ml of water was slowly added thereto at 0°C. The resulting solution was stirred for 5 hours at the room temperature and solid was filtered through celite. The filtrate was evaporated under reduced pressure and then the residual product was purified by a silica gel column chromatography (chloroform : methanol (10:1)) to give 10.4g of the above title compound (yield: 75%).

^{1}H-NMR($CDCl_3$ + DMSO-d_6, δ): 4.58(2H, d), 4.67(2H, d), 5.13(1H, s), 5.30(1H, s), 7.34(1H, m), 7.45(1H, d), 8.45(1H, d)

3) Preparation of 2,3-dichloromethylpyridine hydrochloride

13.9 g of 2,3-dihydroxymethylpyridine and thionylchloride were evaporated under reduced pressure to give 21.2g of the above title compound in yellow solid (yield: 99%).

^{1}H-NMR($CDCl_3$ + DMSO-d_6, δ): 5.10(2H, s), 5.15(2H, s), 7.81(1H, m), 8.15(1H, m), 8.15(1H, d), 8.95(1H, d)

4) Preparation of 2,3-dihydro-2-p-toluene sulfonyl-1H-pyrrolo[2.3.c]pyridine

A solution prepared by suspending 0.9g of 60% sodiumhydride in 50ml of dried dimethylformamide was slowly added dropwise over 2 hours to a solution prepared by dissolving 3.5g of *p*-toluenephosphenylamide in 20ml of dried dimethylformamide. The reacting mixture was stirred for 1 hour at the room temperature and then stirred again for 1 hour at the temperature between 65 and 70°C. A solution prepared by dissolving 2.13g of 2,3-dichloromethylpyridine in 3ml of dried dimethylformamide was added to the reaction mixture. The resulting mixture was stirred for 3 hours at the same temperature and 20ml of water was added thereto. The solvent was evaporated off under reduced pressure. 20ml of water was added again to the mixture, and the resulting mixture was saturated with sodium hydroxide and extracted with 100ml of ethylacetate. The extracted solution was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residual product was purified by a silica gel column chromatography (nucleic acid-ethylacetate (1:2)) to give 1.8g of the above title compound (yield: 65%).

^{1}H-NMR($CDCl_3$, δ): 2.45(3H, s), 4.65-4.68(4H, d), 7.15(1H, m), 7.35(3H, d, d), 7.81(2H, m), 8.46(1H, d)

5) Preparation of 2,3-dihydro-1H-pyrrolo[2.3.c]pyridine dihydrobromide

74g of 2,3-dihydro-2-*p*-toluene sulfonyl-1H-pyrrolo[2.3.c.]pyridine was put into 20ml of 48% hydrobromide, and 1.75g of phenol and 9.18ml of propionic acid was added thereto and then the reaction mixture was refluxed for 48 hours. The reaction mixture was evaporated under reduced pressure and 30ml of water was added to. The water layer was washed with ethylacetate and then water soluble layer was concentrated and stood in a refrigerator to give 2.23g of the above title compound (yield: 79%).

^{1}H-NMR(DMSO-d_6, δ): 5.24(4H, δ), 7.85(1H, m), 8.20(1H, d), 8.90(1H, d)

6) Preparation of *cis*-piperidinopyrrolidine dihydrobromide

1.42g of 2,3-dihydro-1H-pyrrolo[2.3.c]pyridine hydrobromide was dissolved in 30ml of methanol and the mixture was suspended with 1g of 10% Pd/C. The resulting solution was hydrogenated by Parr hydrogenation reactor (initial hydrogen pressure: 60psi) to debenzylate. After the reaction was finished, the reaction solution was filtered through celite and the solvent was evaporated *in vacuo* to give 1.42g of the above title compound (yield: 99%).

^{1}H-NMR(DMSO-d_6, δ): 1.51-1.94(5H, m), 2.71-3.12(7H, m)

Example 4: Preparation of *cis*-3-methyl-piperidinopyrrolidine dihydrobromide

According to the same method as i), ii), iii), iv), v) and vi) of Example 3, 28.1g of 5-methyl-2,3-dicarboxypyridine was used to give 8.88g of the above title compound (total yield: 30%).

^{1}H-NMR(DMSO-d_6, δ): 1.2(4H, m), 1.50-1.91(5H, m), 2.74-3.01(7H, m), 4.10(1H, m), 7.7(1H, dxd), 8.6(1H, s)

Example 5: Preparation of 1-cyclopropyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-8-chloro- 1,4-dihydroquinoline-4-oxo-3-carboxylicacid

300mg of 1-cyclopropyl-6,7-difluoro-1,4-dihydroquinoline-4-oxo-3-carboxylic acid and 210mg of *trans*-piperidinopyrrolidine dihydrochloride were suspended in 10ml of anhydrous acetonitrile and 0.18ml of DBU was added thereto. The reaction mixture was refluxed for 6 hours and cooled to the room temperature. The produced solid was filtered and washed with acetonitrile to give 405.5mg of the above title compound (yield: 100%).

^{1}H-NMR(DMSO-d_6, δ): 1.22(4H, m), 1.61-2.01(5H, m), 2.74-3.01(7H, m), 4.08(1H, m), 7.56(1H, dxd), 8.61(1H, s)

Example 6: Preparation of 1-cyclopropyl-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid

283mg of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydroquinoline-4-oxo-3-carboxylic acid and 210mg of *trans*-piperidinopyrrolidine dihydrochloride were treated according to the same method as that of Example 5 to give 327mg of the above title compound (yield: 84%).

^{1}H-NMR(DMSO-d_6, δ): 1.2(4H, m), 1.50-1.91(5H, m), 2.74-3.01(7H, m), 4.10(1H, m), 7.7(1H, dxd), 8.6(1H, s)

Following compounds may be prepared by the process similar to that described in Example 5.

1-cyclopropyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4dihydroquinoline-4-oxo-3-carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid;

1-cyclopropyl-5-methyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid;

1-cyclopropyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-8-methoxy-1,4-dihydroquinoline-4-oxo-3-carboxylic acid;

1-cyclopropyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydro-4-oxo-1,8-naphthyridin-3-carboxylic acid;

1-(2,4-difluorophenyl)-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydro-4-oxo-1,8-naphthyridin-3-carboxylic acid;

9-fluoro-10-[(*trans*-piperidinopyrrolidine)-8-yl]-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]-benzooxazine-6-carboxylic acid;

1-cyclopropyl-6,8-difluoro-7-[(3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid;

1-cyclopropyl-6-fluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-8-chloro-1,4-dihydroquinoline-4-oxo-3-carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0] nonane)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid;

1-cyclopropyl-5-methyl-6-fluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid;

1-cyclopropyl-6-fluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-8-methoxy-1,4-dihydroquinoline-4-oxo-3-carboxylic acid;

1-cyclopropyl-6-fluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-1,4-dihydro-4-oxo-1,8-naphthyridin-3-carboxylic acid; and

9-fluoro-10-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]-benzooxazine-6-carboxylic acid.

Example 7: <u>Preparation of 1-cyclopropyl-3-nitroacetyl-6-fluoro-8-chloro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride</u>

183mg of nitromethane was dissolved in 10ml of tetrahydrofuran and 120mg of 60% NaH was suspended in the mixture. The resulting solution was stirred for 3 hours at 40°C. 403.5mg of 1-cyclopropyl-6-fluoro-8-chloro-7-[(*trans*-2-(N-*t*-

butoxycarbonyl)piperidinopyrrolidine)-8-yl]-oxo-1,4-dihydroquinoline-3-carboxylic acid, 324mg of CDI and 10ml of chloroform were put into the above solution. The resulting solution was stirred under reflux for 12 hours and the solvent was evaporated under reduced pressure. The produced residue was added to 10ml of THF and the mixture was stirred under reflux for 4 hours. The reaction solvent was evaporated under reduced pressure and the residue was suspended in 20ml of water. The suspension was neutralized with acetic acid and extracted with ethylacetate (20ml x 3). The extracted solution was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The produced residue was purified by column chromatography ($CHCl_3$: MeOH = 9 : 1) to give 389mg of 1-cyclopropyl-3-nitroacetyl-6-fluoro-8-chloro-7-[(*trans*-2-(N-*t*-butoxycarbonyl)piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline. This compound was put into 5ml of 10% methanol solution of hydrogen chloride and the mixture was stirred for 4 hours at room temperature and then 5ml of ethylether was added thereto. The produced solid was filtered and dried under reduced pressure to give 335mg of the above title compound (yield: 64%).

^{1}H-NMR(DMSO-d_6, δ): 1.22(4H, m), 1.01-1.98(5H, m), 2.78-3.08(7H, m), 4.06(1H, m), 6.18(2H, s), 7.74(1H, dxd), 8.78(1H, s)

Example 8: Preparation of 1-cyclopropyl-3-nitroacetyl-6-fluoro-8-methoxy-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride

497mg of 1-cyclopropyl-6-fluoro-8-methoxy-7-[(*trans*-2-(N-*t*-butoxy carbonyl)piperidinopyrrolidine)-8-yl]-oxo-1,4-dihydroquinoline-3-carboxylic acid were treated according to the same method as that of Example 7 to give 327mg of the title compound (yield: 74%).

^{1}H-NMR(DMSO-d_6, δ): 1.20(4H, m), 1.51-1.91(5H, m), 2.70-3.04(7H, m), 3.86(3H, s), 4.00(1H, m), 6.16(2H, s), 7.86(1H, d), 8.84(1H, s)

Following compounds may be prepared by the process similar to that described in Example 7.

1-cyclopropyl-3-nitroacetyl-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride;

1-cyclopropyl-3-nitroacetyl-5-amino-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride;

1-(2,4-difluoro)phenyl-3-nitroacetyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine hydrochloride;

1-cyclopropyl-3-nitroacetyl-6,8-difluoro-7-[(*trans*-2,8-diazabicyclo[4.3.0]nonane-3-methyl)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride; and

1-cyclopropyl-3-(diethoxycarbonyl)acetyl-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride.

1-cyclopropyl-3-(dimethoxycarbonyl)acetyl-6-fluoro-8-methoxy-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride.

Example 9: Preparation of 1-cyclopropyl-3-nitroacetyl-6-fluoro-8-methoxy-7-[(*cis*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride

1) Preparation according to Process (B)

497mg of 1-cyclopropyl-6-fluoro-8-methoxy-7-[(*cis*-2-(N-*t*-butoxycarbonyl) piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylicacidweretreated according to the same method as that of Example 7 to give 314mg of the above title compound (yield: 71%).

^{1}H-NMR(DMSO-d_6, δ): 1.18(4H, m), 1.57-2.00(5H, m), 2.70-3.04(7H, m), 3.86(3H, s), 4.00(1H, m), 6.18(2H, s), 7.86(1H, d), 8.84(1H, s)

2) Preparation according to Process (C)

i) Preparation of 1-cyclopropyl-3-nitroacetyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline

566mg of 1-cyclopropyl-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 648mg of CDI were put into 20ml of THF and the mixture solution is stirred under reflux for 24 hours (A solution). 366mg of nitromethane was mixed in 5ml of THF and 240mg of 60% NaH added thereto. The mixture solution was stirred for 24 hours at room temperature and the above A solution was added thereto. The resulting solution was stirred under reflux for 14 hours. The reaction mixture was cooled and the solvent was evaporated under reduced pressure. The produced residue was purified by column chromatography (nucleic acid : ethylacetate = 5 : 1) to give 450mg of the above title compound (yield: 69%).

^{1}H-NMR(DMSO-d_6, δ): 1.20(4H, m), 3.62(3H, s), 4.00(1H, m), 6.12(2H, s), 7.67(1H, d), 8.60(1H, s)

ii) Preparation of 1-cyclopropyl-3-nitroacetyl-6-fluoro-8-methoxy-7-[(*cis*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinolinehydrochloride

338mg of 1-cyclopropyl-3-nitroacetyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline and 310mg of *cis*-piperidinopyrrolidine were dissolved in 10ml of acetonitrile. 310mg of alumina were added thereto and the mixture was stirred for 10 hours at 60°C. The reaction mixture was evaporated under reduced pressure and the produced residue was suspended in methanol and the mixture solution was stirred under reflux and filtered. The filtrate was collected and evaporated under reduced pressure. The produced residue was put into 15ml of 10% solution of HCl-methanol and the mixture solution was stirred for 2 hours at room temperature. 15ml of ethylether was added thereto and the resulting solution was filtered to give 296mg of the above title compound (yield: 67%).

^{1}H-NMR(DMSO-d_6, δ): 1.18(4H, m), 1.57-2.00(5H, m), 2.70-3.04(7H, m), 3.86(3H, s), 4.00(1H, m), 6.18(2H, s), 7.86(1H, d), 8.84(1H, s)

Following compounds may be prepared by the process similar to that described in Example 9.

1-cyclopropyl-3-(diethoxycarbonyl)acetyl-6-fluoro-8-chloro-7-[(*cis*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochlorid e;

1-cyclopropyl-3-nitroacetyl-6,8-difluoro-7-[(*cis*-2,8-diazabicyclo[4.3.0]nonane-3-methyl)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride; and

1-cyclopropyl-3-(dimethoxycarbonyl)acetyl-6-fluoro-8-methoxy-7-[(*cis*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride.

Comparative Example 1: Preparation of 1-cyclopropyl-6-fluoro-8-methoxy-7-[(*cis*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

295mg of 1-cyclopropyl-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxo-3-carboxylic acid and 210mg of *cis*-piperidinopyrrolidine dihydrochloride were treated according to the same method as that of Example 5 to give 324mg of the above title compound (yield: 81%).

^{1}H-NMR($CDCl_3$, δ): 1.14-1.22(4H, m), 1.51-1.91(5H, m), 2.71-2.98(7H, m), 3.82(3H, s), 4.00(1H, m), 7.84(1H, d), 8.80(1H, s)

Comparative Example 2: Preparation of 1-cyclopropyl-6,8-difluoro-7-[(*cis*-piperidinopyrrolidine-3-methyl)-8-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

283mg of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydroquinoline-4-oxo-3-carboxylic acid and 232mg of *cis*-3-methylpiperidinopyrrolidine dihydrochloride were treated according to the same method as that of Example 5 to give 280mg of the above title compound (yield: 71%).

^{1}H-NMR($CDCl_3$, δ): 1.20(4H, m), 1.56-1.92(8H, m), 2.70-3.00(6H, m), 4.00(1H, m), 7.72(1H, d), 8.68(1H, s)

In vitro antibacterial activity test

The results of *in vitro* antibacterial activity test are shown in Tables 1 and 2. The numbers in Tables represent the minimal inhibitory concentration (MIC, μg/ml) of the corresponding strains and MIC was determined in accordance with the agar culture medium two-fold dilution method by using a Mueller-Hinton agar.

Hoechst standard strains were used. The strains having 10^7 CFU/*ml* were inoculated on the culture medium, and the growth of the strains was observed after incubating them at 37°C for 18 hours, in which ciprofloxacin was used as a control.

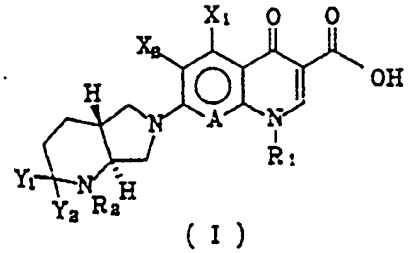
Table 1: *In vitro* antibacterial activity test (MIC, *ug/ml*)

Strain	A	B	C	D	Ciprofloxacin
Streptococcus pyogenes 308A	0.391	0.781	0.781	1.563	3.125
Streptococcus pyogenes 77A	0.098	0.195	0.391	0.391	0.781
Streptococcus faecium MD 8b	0.098	0.195	0.391	0.391	0.781
Staphylococcus aureus SG 511	0.025	0.098	0.098	0.195	0.195
Staphylococcus aureus 285	0.025	0.098	0.025	0.391	0.391
Staphylococcus aureus 503	0.025	0.195	0.025	0.391	0.781
Escherichia coli O 78	<0.002	<0.025	<0.002	0.049	<0.002
Escherichia coil DC 0	0.195	0.391	0.195	0.195	0.195
Escherichia coil DC 2	0.013	0.098	0.098	0.098	0.098
Escherichia coil TEM	0.007	0.049	0.004	0.098	0.007
Escherichia coil 1507E	0.025	0.049	0.025	0.098	0.007
Pseudomonas aeruginosa 9027	0.781	0.781	0.781	1.563	0.391
Pseudomonas aeruginosa 1592E	0.781	0.781	0.781	0.781	0.195
Pseudomonas aeruginosa 1771	0.781	1.563	0.781	0.781	0.195
Pseudomonas aeruginosa 1771M	0.195	0.391	0.391	0.391	0.049
Salmonella typhimurium	<0.002	0.049	0.007	0.098	0.007
Klebsiella aerogenes 1082E	<0.002	0.098	0.049	0.049	<0.002
Klebsiella aerogenes 1552E	0.049	0.098	0.013	0.049	0.013
Enterobacter cloacae P 99	0.004	0.025	0.004	0.013	0.007
Enterobacter cloacae 1321E	<0.002	0.013	<0.002	0.013	<0.002

A: The compound of Example 5
B: The compound of Example 7
C: The compound of Example 8
D: The compound of Example 9

What is claimed is:

1. Novel quinolone derivatives of Formula (I):



(I)

wherein,

X_1 represents hydrogen, amino, halogen, or lower alkyl;

X_2 represents hydrogen or halogen;

Y_1 and Y_2 each represents hydrogen, or lower alkyl (C_{1-3}) group;

R_1 represents a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms or a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms which is substituted with a halogen atom, a phenyl group or a phenyl group substituted with one or two halogen atoms;

R_2 represents hydrogen, or lower alkyl: and

A represents nitrogen atom or -C=,

in which Y represents hydrogen, halogen, lower alkyl or alkoxy or together with R_1 forms $-CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-OCH_2CH_2-$, $-OCH_2CH(CH_3)-$, $-SCH_2CH_2-$, or $-SCH_2CH(CH_3)-$.

2. Compounds of Claim 1 wherein the compounds of Formula (I) is one of the following compounds;

1-cyclopropyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-8-chloro-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

1-cyclopropyl-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

1-cyclopropyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4dihydroquinoline-4-oxo-3-carboxylic acid,

1-cyclopropyl-5-amino-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

1-cyclopropyl-5-methyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

1-cyclopropyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-8-methoxy-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

1-cyclopropyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydro-4-oxo-1,8-naphthyridin-3-carboxylic acid,

1-(2,4-difluorophenyl)-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-1,4-dihydro-4-oxo-1,8-naphthyridin-3-carboxylic acid,

9-fluoro-10-[(*trans*-piperidinopyrrolidine)-8-yl]-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]-benzooxazine-6-carboxylic acid,

1-cyclopropyl-6,8-difluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

1-cyclopropyl-6-fluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-8-chloro-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

1-cyclopropyl-5-amino-6,8-difluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

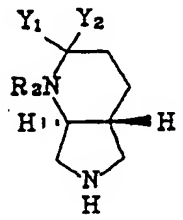
1-cyclopropyl-5-methyl-6-fluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

1-cyclopropyl-6-fluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-8-methoxy-1,4-dihydroquinoline-4-oxo-3-carboxylic acid,

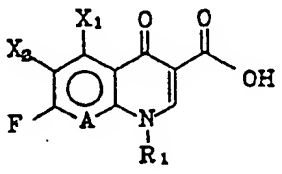
1-cyclopropyl-6-fluoro-7-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-1,4-dihydro-4-oxo-1,8-naphthyridin-3-carboxylic acid,

9-fluoro-10-[(*trans*-3-methyl-2,8-diazabicyclo[4.3.0]nonane)-8-yl]-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]-benzooxazine-6-carboxylic acid.

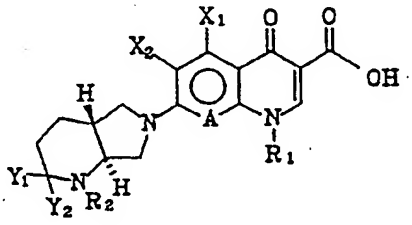
3. A process for preparing compounds of Formula (I) comprising condensing optionally protected *trans*-2,8-diazabicyclo [4.3.0]nonane derivatives of formula (II) with the compound of formula (VI-1) in a solvent, in the presence of an inorganic base such as calcium carbonate and the like or an organic base such as diazabicyclo[5.4.0]undecene (DBU), pyridine, triethylamine and the like:



(II)



(VI-1)

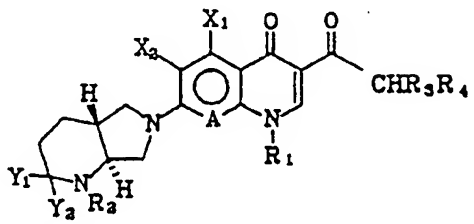


(I)

wherein,

X_1, X_2, Y_1, Y_2, R_1, R_2, and A are the same as defined in Claim 1 or R_2 is a protecting group, and thereafter optionally deprotecting.

4. Novel quinolone derivatives of Formula (III):



(III)

wherein,
X_1, X_2, Y_1, Y_2, R_1, R_2, and A are the same as defined in Claim 1; and
R_3, and R_4 each represents hydrogen, nitro group, nitryl group, methoxycarbonyl group, or ethoxycarbonyl group.

5. Compounds of Claim 4 wherein the compounds of Formula (III) is one of the following compounds;

1-cyclopropyl-3-nitroacetyl-6-fluoro-8-chloro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride,

1-cyclopropyl-3-nitroacetyl-6-fluoro-8-methoxy-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride,

1-cyclopropyl-3-nitroacetyl-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride,

1-cyclopropyl-3-nitroacetyl-5-amino-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride,

1-(2,4-difluoro)phenyl-3-nitroacetyl-6-fluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine hydrochloride,

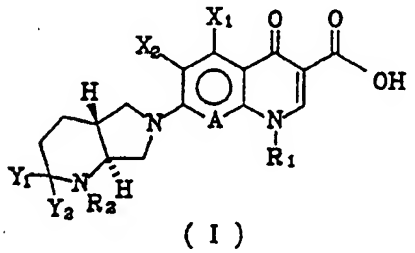
1-cyclopropyl-3-nitroacetyl-6,8-difluoro-7-[(*trans*-2,8-diazabicyclo[4.3.0]nonane-3-methyl)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride,

1-cyclopropyl-3-(diethoxycarbonyl)acetyl-6,8-difluoro-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride,

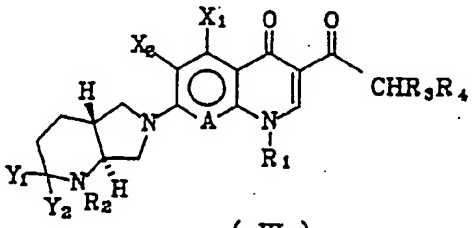
1-cyclopropyl-3-(dimethoxycarbonyl)acetyl-6-fluoro-8-methoxy-7-[(*trans*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride.

6. A process for preparing compounds of Formula (III) comprising reacting compound of formula (I) with an activating agent such as carbodiimidazole (CDI) in the presence of a solvent such as chloroform, tetrahydrofuran (THF) and the like; and

then stirring together with solution prepared by treating nitromethane, diethylmalonate, dimethylmalonate, ethylnitrylacetate with a base such as sodium hydride, calcium carbonate, sodium carbonate in the presence of a solvent such as tetrahydrofuran, and the like:



(I)

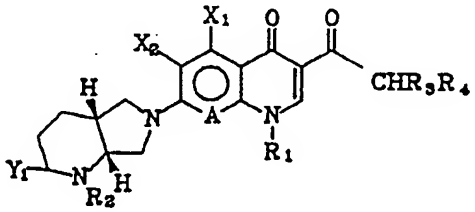


(III)

wherein,

X_1, X_2, Y_1, Y_2, R_1, R_2, R_3, R_4, and A are the same as defined in Claim 3 and thereafter optionally interconverting R_3 and R_4.

7. Novel quinolone derivatives of Formula (IV):



(IV)

wherein,

X_1, X_2, Y_1, R_1, R_2, R_3, R_4 and A are the same as defined in Claim 3.

8. Compounds of Claim 7 wherein the compounds of Formula (IV) is one of the following compounds;

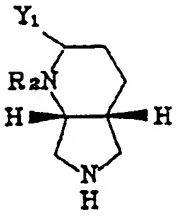
1-cyclopropyl-3-nitroacetyl-6-fluoro-8-methoxy-7-[(*cis*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride,

1-cyclopropyl-3-(diethoxycarbonyl)acetyl-6-fluoro-8-chloro-7-[(*cis*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride,

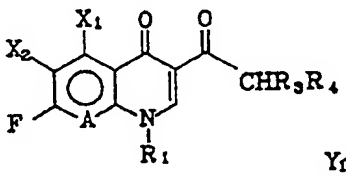
1-cyclopropyl-3-nitroacetyl-6,8-difluoro-7-[(*cis*-2,8-diazabicyclo[4.3.0]nonane-3-methyl)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride,

1-cyclopropyl-3-(dimethoxycarbonyl)acetyl-6-fluoro-8-methoxy-7-[(*cis*-piperidinopyrrolidine)-8-yl]-4-oxo-1,4-dihydroquinoline hydrochloride.

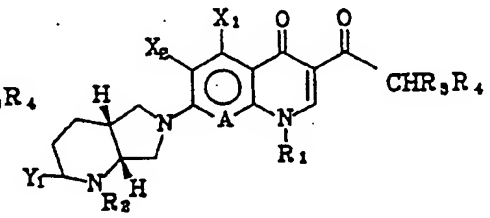
9. A process for preparing novel quinolone derivatives of Formula (IV) comprising stirring optionally protected *cis*-2,8-diazabicyclo[4.3.0]nonane derivatives of formula (V) with the compound of formula (IV-2) in a solvent in the presence of basic, neutral, or acidic alumina:



(V)



(VI-2)



(IV)

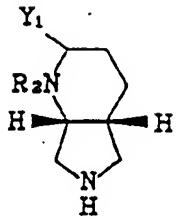
wherein,

X_1, X_2, Y_1, R_1, R_2, R_3, R_4 and A are the same as defined in Claim 3 or R_2 is a protecting group, and thereafter optionally deprotecting and interconverting R_3 and R_4..

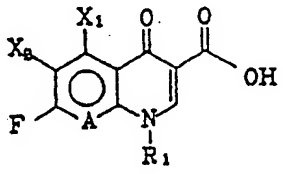
10. A process for preparing novel quinolone derivatives of Formula (IV) comprising following steps:

(1) activating the *cis*-isomer of a compound of formula (I) with an activating agent such as carbodiimidazole in the presence of a solvent such as chloroform, tetrahydrofuran; and

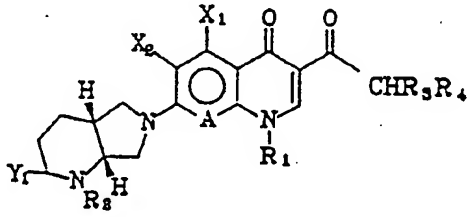
(2) stirring the mixture of step (1) together with solution prepared by treating nitromethane, diethylmalonate, dimethylmalonate, ethylnitrylacetate with a base such as sodium hydride, calcium carbonate, sodium carbonate in the presence of a solvent such as tetrahydrofuran, and the like:



(V)



(VI-1)

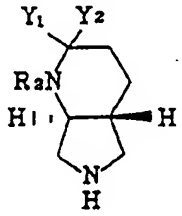


(IV)

wherein,

X_1, X_2, Y_1, R_1, R_2, R_3, R_4, and A are the same as defined in Claim 3 and thereafter optionally deprotecting and interconverting R_3 and R_4.

11. Novel *trans*-2,8-diazabicyclo[4.3.0]nonane derivatives of formula (II):



(II)

wherein,

Y_1, Y_2, and R_2 are the same as defined in Claim 1.

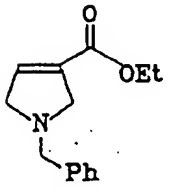
12. A process for preparing novel *trans*-2,8-diazabicyclo[4.3.0]nonane derivatives of formula (II) comprising the following steps:

(1) reacting compound of formula (VII) or an alternative N-protected form with ß-alanine derivatives of formula (XI) in the presence of ethanol to give compound of formula (VIII);

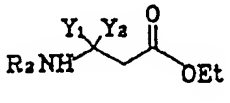
(2) cyclizating the compound of formula (VIII) with base for example alkoxide such as sodium ethoxide or potassium *t*-butoxide to give compound of formula (IX);

(3) reducing the carbonyl group in compound of formula (IX) to a methylene group e.g. tosylhydrazine in a solvent of ethanol or methanol to obtain tosylhydrazone and then, by reducing the resulting compound with sodium shanobrohydride to give compound of formula (X); and

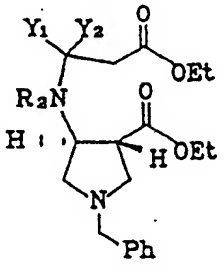
(4) deprotecting the compound of formula (X) for example in a solvent such as methanol in the presence of a catalyst such as palladium or platinum;



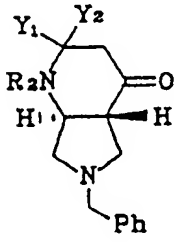
(VII)



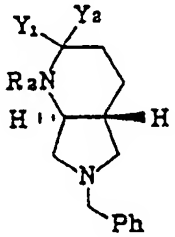
(XI)



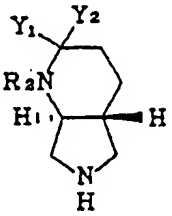
(VIII)



(IX)



(X)



(II)

wherein,

Y_1, Y_2, and R_2 are the same as defined in Claim 1.

13. A process for preparing novel *trans*-2,8-diazabicyclo[4.3.0]nonane derivatives of formula (II) comprising the following steps:

(1) reacting compound of formula (XII) or alternative protected form with ß-alanine derivatives of formula (XI) to give *tran s*isomer of formula (XIII);

(2) converting the resulting hydroxy group to carboxy ester e.g. by

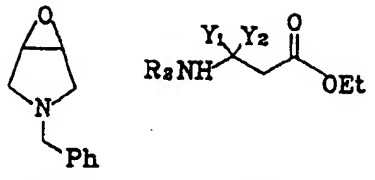
(a) reacting *trans* isomer of formula (XIII) with methansulfonyl chloride and lithium chloride in a solvent such as methylene chloride or chloroform in the presence of an organic base such as triethylamine or diisopropylethylamine to give *cis* isomer of formula (XIV);

(b) reacting *cis* isomer of formula (XIV) with potassium cyanate or sodium cyanate in a solvent to give *trans* isomer of formula (XV);

(3) cyclizating the compound of formula (XVI) for example with alkoxide such as sodium ethoxide or potassium *t*-butoxide at room temperature in the aromatic solvent such as benzene, toluene to give compound of formula (IX);

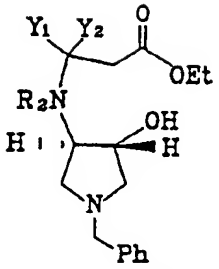
(4) reducing the compound of formula (IX) for example with zinc amalgam in the presence of hydrochloric acid to give compound of formula (X); and

(5) deprotecting the compound of formula (X) in a solvent such as methanol in the presence of a catalyst such as palladium or platinum;

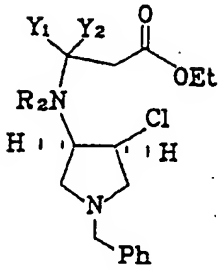


(XII)

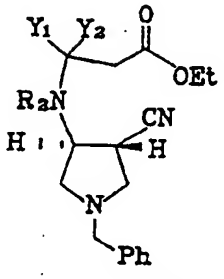
(XI)



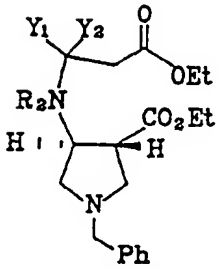
(XIII)



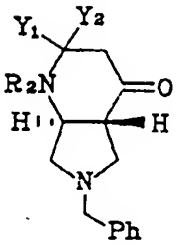
(XIV)



(XV)



(XVI)



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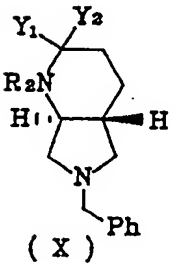

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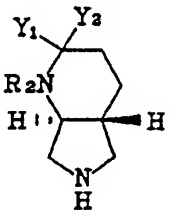


(II)

wherein,

Y_1, Y_2 and R_2 are the same as defined above.

14. A process for preparing *cis*-2,8-diazabicyclo[4.3.0]nonane derivatives of the formula (V) comprising the following steps:

(1) suspending pyridine derivatives of formula (XVII) in a solvent such as methanol and adding thionylchloride thereto and then stirring the resulting compound under reflux to give the corresponding ester compound such as of formula (XVIII);

(2) reducing the compound of formula (XVIII) in a solvent such as ethylether or THF to give alcohols of formula (XIX);

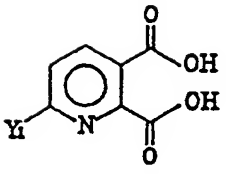
(3) chlorinating, brominating, or methane sulfonylating alcohols of formula (XIX) to give compound of formula (XX);

(4) cyclising the compound of formula (XX) for example with tosylimide and sodium hydride in a solvent such as DMF to give cyclized compound of formula (XXI);

(5) hydrolyzing the compound of formula (XXI) for example with 48% of hydrobromic acid to give amines of formula (XXII);

(6) reacting amine compounds of formula (XXII) with R_2I such as methane iodide and acid anhydrous in a suitable solvent such as methylene chloride or ethyl alcohol to give salts of pyridine of formula (XXIII); and

(7) hydrogenating the compound of formula (XXIII) in a suitable solvent such as methanol or ethanol in the presence of a catalyst such as palladium or platinum;



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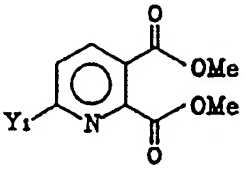

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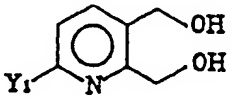

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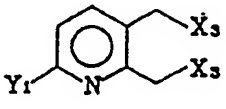

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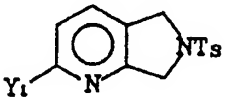

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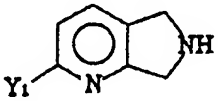

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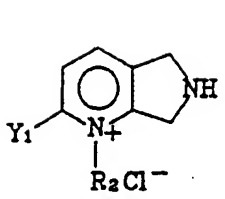

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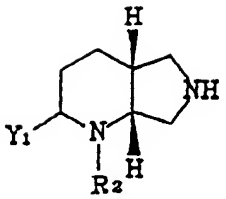

(V)

wherein,

X_3 represents chloro, bromo, or methanesulfonyloxy group; and

Y_1 and R_2 are the same as defined in Claim 1.

15. A pharmaceutical composition which contains a compound or pharmaceutically acceptable salts of: Formula (I) according to Claim 1; Formula (III) according to Claim 3; or Formula (IV) according to Claim 5, as an active ingredient in an effective amount.

16. A compound or pharmaceutically acceptable salts of: Formula (I) according to Claim 1; Formula (III) according to Claim 3; or Formula (IV) according to Claim 5, for use as an antibacterial agent in a method for therapeutic treatment of the human or animal body.

17. A method for the treatment of bacterial infection characterized in that a pharmaceutical composition according to Claim 12 is administered to a host in the need of such treatment in the therapeutically effective amount.

18. Use of a compound or pharmaceutically acceptable salts of: Formula (I) according to Claim 1; Formula (III) according to Claim 3; or Formula (IV) according to Claim 5, for the preparation of an antibacterial medicament.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 94/00005

A. CLASSIFICATION OF SUBJECT MATTER

IPC[5]: C 07 D 487/18, 519/00, 471/04; A 61 K 31/47, 31/435, 31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[5]: C 07 D 487/00, 519/00, 471/00, 215/00; A 61 K 31/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A2, 0 266 576 (BRISTOL-MYERS COMPANY) 11 May 1988 (11.05.88), claims 1-6, 21-23; abstract; page 15, lines 25-53.	1,3,15-18
A	DE, A1, 3 514 076 (TOYAMA CHEMICAL CO.LTD.) 31 October 1985 (31.10.85), claims 1,2,7,38-39,49.	1,3,15-18
A	DE, A1, 3 632 222 (BAYER AG) 07 April 1988 (07.04.88), abstract; claim 1.	1,15-18
A	DE, A1, 4 032 560 (BAYER AG) 16 April 1992 (16.04.92), claims 1-3, 7-10.	1,3,15-18
A	US, A, 5 140 033 (M. SCHRIEWER ET AL.) 18 August 1992 (18.08.92), columns1-8; column 25, lines 6-9; columns 27, 28,37,38; examples 1,3,6,7.	1,3,11,15-18
A	EP, A1, 0 393 400 (WAKANUGA SEIYAKU KABUSHIKI KAISHA) 24 October 1990 (24.10.90), claims 1,13,18; page 4, lines 15-17; page 5, formula (m).	1,3,11,15-18
A	DE, A1, 3 906 365 (BAYER AG) 18 January 1990 (18.01.90), abstract; claims 1-4,8,9; examples 13-15, 22-25, 31-33, 49-51,53; page 6, lines 36-53; page 17, lines 25-28.	1,3,11,15-18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 March 1994 (08.03.94)	04 May 1994 (04.05.94)

Name and mailing address of the ISA/ AT	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna	Mazzucco e.h.
Facsimile No. 1/53424/535	Telephone No. 1/5337058/33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 94/00005

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17 (please see remark)
because they relate to subject matter not required to be searched by this Authority, namely:

Remark:
Although claim 17 is directed to a method of treatment of the human or animal body by therapy the search has been carried out and based on the alleged effects of the composition (Rule 39.1(iv) PCT). The relevant documents are listed in the search report.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 94/00005

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A2 266576	11-05-88	CN A 87106925	14-09-88
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 94/00005

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 94/00005

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